

The affective and neural correlates of heroin vs. cocaine use in addiction are influenced by environmental setting but in opposite directions

Article (Accepted Version)

De Pirro, Silvana, Galati, Gaspare, Pizzamiglio, Luigi and Badiani, Aldo (2018) The affective and neural correlates of heroin vs. cocaine use in addiction are influenced by environmental setting but in opposite directions. *Journal of Neuroscience*, 38 (22). pp. 5182-5195. ISSN 0270-6474

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1 Title: The affective and neural correlates of heroin vs. cocaine use in addiction are
2 influenced by environmental setting but in opposite directions
3

4 Abbreviated Title: Opposite effects of setting on cocaine vs. heroin

5 by

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22 Number of pages: 43

23 Number of figures: 6

24 Number of tables: 4

25 Abstract: 249 words

26 Significant Statement: 118 words

27 Introduction: 647 words

28 Discussion: 1500 words
29
30

31 Conflict of Interest:

32 The Authors have no conflict of interest to declare
33

34 Acknowledgements:
35

36 A special thank to Giovanni Iavarone for his help with the organization of the fMRI
37 study. We also thank Massimo Barra, Ettore Rossi, and the staff of Villa Maraini, as
38 well as the participants for their time and commitment. We are very grateful to Drs.
39 Kent Berridge, Cecilia Guariglia, and Terry Robinson for their insightful comments
40 on an earlier version of the manuscript. This study was supported by funding from
41 the Sapienza University of Rome to G.G. and A.B. (Fondi di Ateneo) and from the
42 University of Sussex to A.B. (SDF).
43

Abstract

Previous studies have shown that individuals with heroin and cocaine addiction prefer to use these drugs in distinct settings: mostly at home in the case of heroin and mostly outside the home in the case of cocaine. Here we investigated whether the context would modulate the affective and neural responses to these drugs in a similar way. First, we used a novel emotional task to assess the affective state produced by heroin or cocaine in different settings, based on the recollections of male and female drug users. Then we used fMRI to monitor neural activity during drug imagery (recreating the setting of drug use) in male drug users. Consistent with our working hypothesis, the majority of participants reported a shift in the affective valence of heroin from mostly pleasant at home to mostly unpleasant outside the home ($p < 0.0001$). The opposite shift was observed for cocaine, that is, most participants who found cocaine pleasant outside the home found it unpleasant when taken at home ($p < 0.0014$). Furthermore, we found a double dissociation, as a function of drug and setting imagery, in BOLD signal changes in the left prefrontal cortex and caudate, and bilaterally in the cerebellum (all p 's < 0.01), suggesting that the fronto-striatal-cerebellar network is implicated in the contextualization of drug-induced affect. In summary, we report that the same setting can influence in opposite directions the affective and neural response to psychostimulants versus opiates in humans, adding to growing evidence of distinct substrates for the rewarding effects of these two drug classes.

67 **Significance Statement**

68

69 The rewarding effects of addictive drugs are often thought to depend on shared
70 substrates. Yet, environmental influences can unmask striking differences between
71 psychostimulants and opiates. Here we used emotional tasks and fMRI to explore the
72 influence of setting on the response to heroin versus cocaine in individuals with
73 addiction. Simply moving from one setting to another significantly decreased heroin
74 pleasure but increased cocaine pleasure, and vice versa. Similar double dissociation
75 was observed in the activity of the fronto-striatal-cerebellar network. These findings
76 suggest that the effects of opiates and psychostimulants depend on dissociable
77 psychological and neural substrates and that therapeutic approaches to addiction
78 should take into account the peculiarities of different drug classes and the settings of
79 drug use.

80

Introduction

Previous studies in individuals with substance use disorder (SUD) have shown that the context in which heroin and cocaine are used can influence their reinforcing effects in a substance-specific manner. When asked where they preferred using these drugs, they indicated distinct settings: heroin was used mostly at home whereas cocaine was used mostly outside the home, regardless of route of administration and social context (Caprioli et al., 2009; Badiani and Spagnolo, 2013). Intravenous self-administration (SA) experiments in the rat yielded similar findings. Rats residing in the SA chambers (which is also their home environment) tend to prefer heroin to cocaine, whereas rats that do not reside in the SA chamber tend to prefer cocaine to heroin (Caprioli et al., 2009). Many aspects of cocaine versus heroin reward appear to be modulated in opposite directions by the setting: drug intake (Caprioli et al., 2007b; 2008), motivation to work for the drug (Caprioli et al., 2007b; 2008; Celentano et al., 2009), drug discrimination (Paolone et al., 2004; Caprioli et al., 2007a), drug-induced ultrasonic vocalizations (Avvisati et al., 2016), and vulnerability to relapse (Montanari et al., 2015). The findings in the rat suggest that the results obtained in humans were not the trivial consequence of a conscious decision to take a sedative drug in a place where one can relax, and an activating drug where one can move around, but reflected fundamental and substance-specific influences of setting on the response to drugs. The question to be addressed here concerns whether such preferences may be due the fact that heroin and cocaine produce different affective states in different settings.

We have proposed that the overall rewarding effects of addictive drugs are the result of a complex interaction between their central and peripheral effects and the

setting of drug use (Badiani, 2013). Cocaine, for example, produces a state of arousal by activating noradrenergic transmission both centrally and peripherally (Billman, 1995; Sofuoglu and Sewell, 2009; Maceira et al., 2014; Antoniazzi et al., 2017). A similar state of physiological arousal usually occurs when individuals are exposed to exciting, potentially dangerous contexts. Thus, when cocaine is taken at home, the exteroceptive information signaling a quiet environment might conflict with the interoceptive information signaling a state of arousal, resulting in a ‘mismatch’ between exteroceptive and interoceptive information. The reverse line of reasoning applies to heroin, which depresses the central nervous system and acts in a complex manner in the periphery producing, among other effects, bradycardia (Haddad and Lasala, 1987; Thornhill et al., 1989; Nilsson et al., 2016). Thus, when heroin is taken outside the home, there is a mismatch between exteroceptive information requiring alertness and vigilance and interoceptive information signaling reduced arousal and relaxation. In summary, the setting of drug use provides an ‘ecological backdrop’ against which the central and peripheral effects of drugs are appraised, and when a mismatch between exteroceptive and interoceptive information is detected, the rewarding effect of the drug is thwarted.

Thus, the first aim of our study was to test the hypothesis that the affective response to heroin and cocaine, as recollected by experienced drug users, would undergo opposite shifts as a function of the setting. In particular, we hypothesized that the positive affective valence of heroin would be greater at home than outside the home, and that the opposite would occur for cocaine.

Our second aim was to begin exploring the neural basis of drug-setting interactions using an emotional imagery task and functional Magnetic Resonance Imaging (fMRI). We expected to observe changes in blood-oxygenation-level

dependent (BOLD) signal in the regions of the memory retrieval network (Bonicci et al. 2016, Kuhl and Chun 2014, Ritcher et al. 2016, Fletcher et al., 1995; Spaniol et al. 2009), and a double dissociation, as a function of drug and setting, in regions implicated in drug reward processing, such as the prefrontal cortex (PFCx) and the striatum, (Volkow et al., 1999; Cox et al., 2009).

Material and Methods

Experiment 1

Participants

Prospective participants with a diagnosis of heroin or cocaine use disorder (DSM-IV or DSM-5) were recruited during their daily visit at the Substance Misuse Services of Villa Maraini (Rome, Italy) and were then screened for the following inclusion criteria: 1) age between 18 and 68 years; 2) fixed residence at the time of regular drug use; 3) good understanding of Italian or English language; 4) no psychoses, or bipolar disorders, or major depressive disorder; 5) no current alcohol dependence (as indicated by a state of inebriation at the moment of recruitment or by treatment for alcohol abuse); 6) no cognitive impairment or state of intoxication such as to preclude informed consent or valid self-report. Before the start of the study, the participants were informed about the structure of the study and in particular that: 1) the questionnaires would focus on their current (or past) heroin and/or cocaine use; 2) the data thus collected would remain anonymous and confidential; 3) they were free to withdraw from the study at any time they wished. After having briefed about the

study, the participants provided informed consent. Procedures and methods were in accordance with the Declaration of Helsinki and were approved by the University of Sussex Science and Technology Cross-Schools Research Ethics Committee (C-REC). Participation in the study was voluntary, and no monetary or non-monetary incentives were offered.

Fifty-three individuals (mean age=37.11, SD=10.42), who identified themselves as females (11) or males (42), participated in the experiment. The sample included 45 heroin and cocaine users, 7 cocaine-only users, and 1 heroin-only user. All of them had a long history of heroin (15.96 years, SD=10.31) and/or cocaine (14.44 years, SD=8.51) use. Table 1 summarizes the socio-demographic characteristics of the sample and basic information about drug use. The majority of the participants (86.79%) had a fixed residence at the time of their enrolment in the study. However, it is important to point out that the information concerning the setting of drug use referred to periods in which the participants had a fixed residence.

Procedures

The emotional state induced by the drug was assessed using a graphic approach based on the Circumplex Model of Affect (Russell, 1980), illustrated in Figure 1A, which posits that all affective states arise from the interaction of two independent neurobiological systems: arousal (along high-low energy continuum) and valence (along a pleasure-displeasure continuum). Our aim was to develop a user-friendly, intuitive test that could be completed rapidly without relying on the cognitive processes required for the verbal description and interpretation of emotional states, which could have represented a confounding factor given the participants' negative

feelings about their own addiction (Dearing et al., 2005; Luoma et al., 2012, 2013). Thus, we created the diagram illustrated in Figure 1B, representing a two-dimensional space of emotional state with arousal on the vertical dimension and valence on the horizontal dimension. Emoticons and colors were added to increase the evocative power of the diagram (Nathanson et al., 2016; Kaye et al., 2017).

The interview took place (during the participants' daily visit for treatment) in a quiet medical room at the Substance Misuse Service "Villa Maraini". Responses were collected by the interviewer and entered into the online survey host Survey-Gizmo (<https://www.surveygizmo.com>) using the offline mode.

At the start of the interview, anonymized demographic data were collected, and the diagram (Fig. 1 B) was explained to the participants following the procedures described by Russell and Mendelsohn (1989). The diagram was presented as a 2-D spatial map of emotional states, with the center of the circle representing a neutral state, (which is not positive or negative). Consequently the participants could position themselves in one of the quadrants according to the following combination: i) top-right yellow quadrant if the emotional state experienced was simultaneously pleasurable and arousing; ii) bottom-right green quadrant if the emotional state was simultaneously pleasurable and sedating; iii) bottom-left blue quadrant if the emotional state was simultaneously unpleasant and sedating; (iv) top-left red quadrant if the emotional state was simultaneously unpleasant and arousing.

The participants were instructed to recall a typical drug experience and to rate the affective state produced by heroin versus cocaine in two settings (at home versus outside the home). Before the interview, they were also instructed to exclude instances of combined heroin and cocaine use ('speedball').

For each combination of drug and setting, the participants were asked to

choose the quadrant that best reflected the affective states experienced while under the influence of the drug. Since we expected that in some case the affective state experienced while under the effect of the drug could not be reduced to a single condition, no restriction was placed on the number of affective states that the participant could report for each combination of set and setting. In 82.7% of cases, the participants indicated a single quadrant, more rarely two quadrants (15.3%) and only in 2% of cases they selected three or four quadrants. In 11.2% of cases, the selection of more than one quadrant resulted in a mixed valence (pleasant and unpleasant at the same time). That is, in 88.8% of cases the valence was either entirely pleasant or entirely unpleasant.

Data analysis

Data were classified and analyzed in order to test two separate hypotheses. The main working hypothesis predicted a complete or partial shift in the affective valence of heroin and cocaine as a function of setting. Thus, the data were arranged in a 2x2 contingency table, and the McNemar's test was used to assess the difference between the two correlated proportions (McNemar, 1947). A more rigorous reading of the working hypothesis would require limiting the analysis to the individuals who experienced heroin-induced sedation in both settings and to those who experienced cocaine-induced activation in both settings. That is, all cases in which there was a discrepancy for the dimension 'arousal' were excluded from this analysis. Also this hypothesis was tested using the McNemar's test. Effect size was estimated by calculating odds ratios (ODs).

The second hypothesis, often surreptitiously incorporated in theoretical and

experimental frameworks, is that all drugs produce ‘pleasure’. For each combination of drug and setting, we calculated the observed frequency of the following three categories: i) pleasant (by combining the frequency of entries for quadrants ‘pleasant-arousing’ and ‘pleasant-sedating’), ii) unpleasant (by combining the frequency of entries for quadrants ‘unpleasant-arousing’ and ‘unpleasant-sedating’), and iii) mixed valence (for all the instances in which both pleasant and unpleasant quadrants were selected). We used the one-sample Kolmogorov-Smirnov test (Massey, 1951) to assess the degree to which the observed frequencies differed from the expected frequencies based on the ‘pleasure’ hypothesis (pleasant:mixed:unpleasant = 1:0:0). We also tested a ‘weak’ version of the ‘pleasure’ hypothesis in which the categories pleasant and mixed were combined (pleasant/mixed:unpleasant = 1:0).

Experiment 2

Participants

Prospective participants (who did no overlap with the participants in Experiments 1) with a diagnosis of heroin or cocaine dependence (DSM-IV) were recruited during their daily visit at the Substance Misuse Services of Villa Maraini and were then screened for the following inclusion criteria: 1) age between 18 and 55 years; 2) heroin and/or cocaine use at least once a week in the past 12 months; 3) fixed residence; 4) no history of neurological disorder or head trauma with loss of consciousness exceeding 30 min; 5) no other contraindication to MRI; 6) no psychoses, or bipolar disorders, or major depressive disorder; 7) no current alcohol

dependence (as indicated by a state of inebriation at the moment of recruitment or by treatment for alcohol abuse); 8) no cognitive impairment or state of intoxication such as to preclude informed consent or valid self-report. Before the start of the study, the participants were informed about the structure of the study and in particular that: 1) they would undergo an imagery procedure during the fMRI scan; 2) the data thus collected would remain anonymous and confidential; 3) they were free to withdraw from the study at any time they wished. After having briefed about the study, the participants provided informed consent. Procedures and methods were in accordance with the Declaration of Helsinki and were approved by the IRCSS Santa Lucia Foundation Ethics Committee. The participants received a flat reimbursement of 30 euro for their time. Refreshments were provided during the pre and post-scanning time.

Twenty-five individuals were recruited initially. Two individuals were excluded because of their inability to focus on imagery during training and one because of signs of distress produced by the scanner noise. Two individuals were excluded before completing the scan because of claustrophobia. Finally, the fMRI data from 1 participant were excluded from further analysis because of technical problems during acquisition.

The sample that completed the study consisted of twenty male individuals (aged 35.35, SD=8.13) with history of both heroin (13.20 ± 6.29 years) and cocaine (15.25 ± 5.74 years) abuse. Demographic information is reported in Table 2.

Procedures

Emotional Imagery

281

282 We adapted an emotional imagery procedure based on previous work by Lang and
283 colleagues (Lang, 1979; Lang et al., 1980) to ask the participants to imagine taking
284 heroin and cocaine in two different real-world settings where they had previously
285 used these drugs.

286

287 *Script.* The scripts for the imagery task were developed based on self-reports collected
288 on occasion of previous studies (Caprioli et al., 2009; Badiani and Spagnolo, 2013)
289 and of pilot interviews. Emotional imagery procedures are capable of eliciting a
290 mental representation that is not simply a picture scanned with the “mind’s eye” but a
291 dynamic scenario based on real-life experience, involving high level cognitive
292 functions such as perception, memory, emotion, and motor control (Rollins et al.,
293 1992; Kosslyn et al., 2001; Owen et al., 2006; Berger and Ehrsson, 2014). Previous
294 studies reported similar neural substrates for imagery and perception, demonstrating
295 that it is possible to induce a subjective experience resembling an actual perceptual
296 experience by using verbal instructions based on an appropriate script (Lang, 1979;
297 Reddy et al., 2010; Cichy et al., 2012; Lee et al., 2012). In agreement with previous
298 studies (Lang, 1979; Lang et al., 1980; Dougherty et al., 1999; Cuthbert et al., 2003;
299 McTeague et al., 2009; Costa et al., 2010), each script was structured to include: i) the
300 instruction to create a mental image; ii) the description of the scenario to be imagined,
301 that is, one of two settings: the participant’s own home (‘home’ condition) and the
302 participant’s habitual club (‘outside-the-home’ condition); iii) the instruction to
303 imagine oneself engaging in heroin or cocaine use (at home or outside the home) ‘as
304 if’ it were really happening.

305 Thus, we created two scripts for the baseline imagery task, in which

participants were asked to visualize themselves relaxing at home or in their usual club, and four scripts for the drug imagery task, one script for each combination of drug and setting: i) cocaine at home, ii) cocaine outside the home, iii) heroin at home, iv) heroin outside the home. The scripts did not include any information specific to the individual; that is, the scripts had a standard format that was applicable to all participants (Table 3). The scripts were then recorded and played during the imagery tasks.

Training. A week prior to the fMRI session, the participants underwent an imagery training session conducted in a quiet room at Villa Maraini. The main aim of the session was to familiarize the participants with the imagery procedure while listening to a recording of the scanner noise through headphones and to enhance the participants' emotional involvement during testing. Indeed, previous studies have shown that imagery training can increase the emotional response during the imagery task (Miller et al., 1987; Sinha, 2009).

The participants were asked to complete the following imagery questionnaires (adapted to Italian by Antonietti and Crespi, unpublished manuscript): 1) Vividness of Visual Imagery Questionnaire (VVIQ; Marks, 1989) in which the participants were instructed to visualize themselves in standard environmental contexts; 2) Vividness of Movements Imagery Questionnaire (VMIQ; Isaac et al., 1986) in which participants were instructed to visualize themselves while performing specific movements; 3) Test of Visual Imagery Control (TVIC; Gordon, 1949), in which the participants were instructed to operate a transformation on a mental image; 4) An adaptation of the Questionnaire on "Imagery induction of emotional state" (Wright and Mischel, 1982), in which participants were instructed to imagine situations associated with a 'positive'

emotional state (serene, happy, surprised and relaxed) or to a ‘negative’ emotional state (hungry, fearful, disgusted, sad). The participants were instructed to close their eyes, to ignore as far as possible the noise of the scanner, to create a mental scenario for each condition (based on hypothetical or real events from their personal life), to imagine ‘living’ this scenario, and finally to rate the vividness of the imagery by assigning a score from 1 (not clear at all) to 5 (perfectly clear) to each item in the questionnaires. The imagery training session lasted approximately 40 min.

Emotional Imagery during the fMRI session. On the day of the fMRI scan, participants underwent a urine drug screen for amphetamine, barbiturates, benzodiazepines, cocaine, methadone, morphine/opiates, methamphetamine, and THC (Drug-Screen Multi 8TC test; nal von minden GmbH, Moers, Germany) at the Substance Misuse Service Villa Maraini (see Table 2). They were then transferred to the Brain Imaging facility of the Santa Lucia Foundation. Sixteen participants took their usual dose of methadone before leaving the clinic. Smokers were allowed to smoke prior to the scan. All the participants were blind to the content of the experimental session.

Before entering the fMRI scanner, the participants received the following instructions by the experimenter:

“You will be asked to imagine yourself in two different settings, specifically to be either at your own home or in your usual club. Your task will be to visualize as vividly as possible the setting in your mind and to focus intensely on this situation as if it were really happening at that moment. You will then be asked to imagine using heroin or cocaine (but not heroin and cocaine combined, that is, no ‘speedball’) in that very same setting. You should try to focus on the effects produced by the drug while

356 in that specific setting.

357 When asked to imagine being at home it is really important that it is your own
358 home. You can imagine being in any part of your home (living room, bedroom,
359 bathroom, kitchen) where you usually take or have taken the drug. If you have never
360 taken that drug in that setting, try to imagine how it would actually be to do so. The
361 imagined event should take place in the evening, at 21:00 hours.

362 When asked to imagine being in a club, it is really important that it is, or has
363 been, your usual club. You can imagine being in any part of the club where you
364 usually take or have taken the drug. If you have never taken that drug in that setting,
365 try to imagine how it would be to actually to do so. The imagined event should take
366 place in the evening, at 21:00 hours.”

367

368 *fMRI session*

369

370 The study design is outlined in Figure 2A. During the fMRI session, each participant
371 underwent a total of eight trials, two for each combination of drug and setting (i.e.,
372 heroin at home, cocaine at home, heroin outside, cocaine outside), in a pseudo-
373 random sequence, counterbalanced across subjects. Subjects were equipped with
374 headphones, and each scan was preceded by audio and video instructions guiding
375 them through the imagery task.

376 Each trial began with a 60-s baseline period, during which the participants
377 were first asked to imagine relaxing either at home or outside the home. Following
378 this period, the participants were asked to imagine taking heroin or cocaine at home or
379 in a club for 120 s. This period was then followed by a 60-s rest period in which the
380 participants were asked to stop the imagery. Immediately after the end of each trial,

the participants rated the vividness of the imagery on using a VAS (visual analogue scale) ranging from 1 ('not vivid at all') to 10 ('perfectly vivid') displayed on a screen, using a push button controller. The graph in Figure 2B depicts the vividness rating from each participant after the imagery period showing no significant differences between the four combinations of drug and setting.

Apparatus and image acquisition

Functional MRI scans sensitive to BOLD contrast were collected using a Siemens Allegra scanner (Siemens Medical Systems, Erlangen, Germany) 3.0 Tesla scanner operating at the Neuroimaging Laboratory, Foundation Santa Lucia. Stimuli were generated by a control computer located outside the MR room, running an in-house software implemented in MatLab (Galati et al., 2008; Sulpizio et al., 2013; Boccia et al., 2015). Instructions were presented simultaneously in audio and video modalities. An LCD video was used to project instructions to a back projector screen mounted inside the MR tube and visible through a mirror located inside the head coil. Presentation timing was synchronized by the acquisition of fMRI images. Responses were given through push button connected to the computer by optic fibers. Head movements were minimized by mild restraint and cushioning.

Functional MRI images were acquired for the entire brain using a gradient echo planar imaging (EPI) sequence covering the whole brain (34 slices, in-plane resolution=3x3 mm, slice thickness=3 mm, inter-slice distance=1.25 mm, repetition time [TR]=2210 ms, echo time [TE]=30 ms, flip angle=70° deg). For each scan, a total of 113 fMRI volumes were acquired. A high-resolution 3D T1-weighted MRI scan was acquired for each subject using a magnetization-prepared rapid gradient

echo sequence (Siemens MPRAGE, 176 slices, in-plane resolution= 0.5 mm, in-plane resolution=0.5x0.5 mm, slice thickness=1 mm, TR=2000 ms, TE=4.38 ms, flip angle=8° deg).

Data analysis

Image analyses were performed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK <http://www.fil.ion.ucl.ac.uk/spm>) implemented in MatLab (MATLAB 2011a, The MathWorks, Inc., Natick, MA, USA). The first four volumes of each scan were discarded to allow for T1 equilibration effects.

Functional time series from each subject were temporally corrected for slice timing, using the middle volume in time as a reference, and then spatially corrected for head movement (realigned), using a least squares approach and a six-parameter rigid-body spatial transformation. The images were then coregistered onto their T1 image and spatially normalized using an automatic nonlinear stereotaxic normalization procedure (final voxel size: 3x3x3 mm) and spatially smoothed with a three dimensional Gaussian filter (6 mm full-width-half-maximum (FWHM). The template image for spatial normalization into a standard stereotaxic space was based on Montreal Neurological Institute (MNI-152) template and conforms to a standard coordinate referencing system (Talairach and Tournoux, 1988).

Images were analyzed using a standard random-effect procedure. The time series of functional MR images obtained from each participant were analyzed separately. The effect of the experimental paradigm was estimated on a voxel by voxel basis, according to the general linear model extended to allow the analysis of fMRI data as a time series. The model included a temporal high-pass filter to remove

low frequency confounds with a period >128 s. Serial correlations in the fMRI time series were estimated with a restricted maximum likelihood (ReML) algorithm assuming the same correlation structure for each voxel, within each scan. The ReML estimates were then used to whiten the data.

Initially, neural activation during the imagery task was modeled as a box-car function spanning the whole duration of the imagery period and convolved with a canonical hemodynamic response function (HRF), chosen to represent the relationship between neuronal activation and blood oxygenation (Friston et al., 1998). Images of subject-specific parameter estimates, which represented activation relative to the baseline, were calculated for each of the four drug imagery scenarios. Inter-trial resting periods were excluded from data analysis due to the potential carryover effects of the imagery task.

Using an “omnibus” F-contrast, we searched for voxels exhibiting a significant increase in BOLD signal during drug imagery (relative to baseline imagery) in any of the four imagery conditions (that is, irrespective of the specific drug-setting combination). The resulting statistical parametric map was corrected for multiple comparisons based on family-wise error rate (FWE) and thresholded at $p=0.05$ corrected at voxel level (see Table 4 and Figure 4).

These initial whole-brain analyses aimed at selecting a map of regions implicated in the drug imagery task. This activation map was then used as a search mask within which to look at modulations induced by drug and setting. We applied a deconvolution approach to the regionally averaged time courses from each region. We modeled each trial as a set of twelve finite impulse response (FIR) basis functions (Burock and Dale, 2000; Ollinger et al., 2001) spanning 10 s each, starting from the onset of the imagery task. Such approach allows for a flexible hemodynamic

response function (HRF) modeling without any assumption on the shape of the HRF in the time period within each trial where the difference in the signal arose, although remaining in the General Linear Model (GLM) framework (Steffener et al., 2010). To directly examine the interactions relevant to our experimental questions, the resulting regional hemodynamic responses were analyzed using a 3-way analysis of variance (ANOVA) with repeated measures on the factors drug (2 levels: heroin vs. cocaine), setting (2 levels: home vs. outside the home), and time (12 levels). Bonferroni's correction ($p' = 1 - (1-p)^{1/22}$) was applied to the resulting p values. Effect size was estimated by calculating partial eta squared (η_p^2) values.

Results

Experiment 1

As illustrated in Figure 1, the affective valence of the drug experience changed as a function of both drug and setting. When heroin was taken at home, the majority of participants reported experiencing a pleasant affective state (89.1%) or a mixed (both pleasant and unpleasant) state (4.3%), whereas only 6.5% reported an unpleasant state. In contrast, when heroin was used outside the home, only 50% of participants reported positive (39.1%) or mixed (10.9%) affective states, whereas the other 50% reported an unpleasant experience. The opposite pattern was observed for cocaine. Cocaine at home produced a pleasurable state only in 26.9% of participants, whereas 61.5% experienced an unpleasant state and 11.6% a mixed state. In contrast, when taken outside the home cocaine produced pleasant or mixed states in the majority of

participants (50% and 17.3%, respectively) whereas 32.7% experienced an unpleasant state.

Within-subject analysis of the data confirmed the main prediction of our working hypothesis. Indeed, the valence of the affective states induced by heroin and cocaine underwent opposite shifts as a function of setting in a sizeable number of participants. In the case of heroin, McNemar's test indicated that the valence was more negative outside the home than at home in 26 participants, whereas the opposite shift was observed only in 1 participants (OR=26; 95%CI=3.53-191.6; $p<0.0001$). In the case of cocaine, the valence was more negative at home than outside the home in 24 participants, whereas the opposite shift was observed only in 6 participants (OR=4; 95%CI=1.63-9.79; $p=0.0014$).

As the working hypothesis further specified that the shift in valence was the result of a mismatch between exteroceptive and interoceptive information, the data were re-analyzed including only the cases in which there was concordance for the vertical dimension (arousal in the case of cocaine, and sedation in the case of heroin). Also this sub-set of data was consistent with the working hypothesis: the McNemar's test indicated opposite shifts in valence, as a function of setting, for heroin (OR=6; 95%CI=1.78-20.37; $p<0.001$) and cocaine (OR=infinity; $p=0.0015$).

A secondary aim of the study concerned the assumption (often, albeit surreptitiously, incorporated in theoretical and experimental frameworks) that all addictive drugs produce a state of 'pleasure'. The Kolmogorov-Smirnov test indicated that the observed frequencies were not significantly different ($p>0.2$) from those expected on the basis of either the strong or the weak version of the 'pleasure' hypothesis (see Data Analysis in the Material and Methods section) only when heroin was used at home. This was not the case for heroin use outside the home and for

cocaine in either setting ($p < 0.0001$ versus either strong or weak version of the ‘pleasure’ hypothesis). In summary, only when heroin was used at home the emotional state induced by the drug was rated as being overall pleasant by the majority of participants. This is not consistent with the idea that the primary reason for drug use is because drugs uniformly produce a pleasurable affective state.

Experiment 2

Overall effect of drug imagery

Table 4 lists the clusters in which whole-brain analysis indicated significant changes in the BOLD signal during drug imagery relative to baseline imagery, for any of the four conditions (i.e., irrespective of drug type and setting). Drug imagery produced significant activation in the left PFCx, (Broadman Area (BA) 6, BA 8, BA 44, BA 45, and BA 46), left supplementary motor area (BA 32), left angular gyrus, left posterior cingulum, and left precuneus. Bilateral activation was evident in the caudate, thalamus, brain stem, inferior temporal gyrus, and cerebellum.

Modulatory effect of setting on drug imagery

When the data from the regions activated by drug imagery (Table 4) were again analyzed for time-dependent interaction of drug and setting in BOLD signal amplitude, we found significant drug x setting x time interaction in the middle frontal gyrus of the left PFCx (BA 44; Fig. 5, central panels), in the left caudate (Fig. 6, left panels), and bilaterally in crus I/II of the cerebellum (Fig. 6, central and right panels).

The results of the statistical analysis are detailed in Table 5. In all these regions, the change in BOLD signal was greater when the participants were asked to imagine taking heroin outside the home and cocaine at home (the less preferred settings), compared to heroin at home and cocaine outside the home (the preferred settings). Indeed, it appears that the divergence in drug-induced BOLD signal, as a function of setting, became progressively larger during the drug imagery task (Fig. 5 and 6), probably because of a progressively greater emotional involvement of the participants. Most important, the η_p^2 values indicated a large effect size (Cohen 1988) for both drug x setting and drug x setting x time interaction in these regions. No main effect of drug or setting was found in these regions (all Bonferroni's corrected p 's > 0.99).

Drug x setting x time interaction was also found in smaller clusters in the left middle frontal gyrus (BA 8 and BA 46; Fig. 5, left and right panels), left precuneus, left temporal cortex, and right brain stem, even though it did not survive Bonferroni's correction (all p 's \geq 0.3).

Imagery Vividness

As shown in Fig. 3B, the subjective vividness of drug imagery was virtually identical for heroin at home (8.17 ± 0.29), heroin outside the home (7.80 ± 0.27), cocaine at home (8.02 ± 0.27), and cocaine outside the home (8.15 ± 0.23), as confirmed by the Friedman's test ($\chi^2 = 3.30$, $p = 0.3$).

Discussion

556

557 We report here two major findings. First, we found that the valence of the affective
558 state produced by heroin and cocaine in individuals with SUD shifts in opposite
559 directions by changing the setting of drug use, heroin being experienced as more
560 pleasant at home than outside the home, and vice versa for cocaine. Second, when an
561 independent sample of individuals with SUD was asked to imagine typical drug
562 taking experiences, a double dissociation, as a function of drug and setting, in BOLD
563 signal was observed in the dorsolateral PFCx, dorsal caudate, and cerebellum.

564

565 **Drug, setting, and affect**

566

567 On the basis of earlier findings in humans and rats (Caprioli et al. 2007a, 2007b,
568 2008, 2009; Testa et al. 2011; De Luca and Badiani 2011; De Luca et al. 2012;
569 Badiani and Spagnolo, 2013), it was proposed that in the presence of a mismatch
570 between exteroceptive information (setting) and interoceptive information generated
571 by central and peripheral drug actions, the affective valence of drug experience would
572 be more negative than in conditions in which there was no such a mismatch (Badiani
573 2013). A particular instance of this theory is represented by the arousal state
574 mismatch hypothesis. To test this hypothesis, we identified two scenarios in which
575 such a mismatch should occur. In one scenario (cocaine at home), the state of arousal
576 produced by cocaine would be at odds with a presumably quiet and safe domestic
577 setting (but not with exciting non domestic settings). In another scenario (heroin
578 outside the home), the sedative effects of heroin would be at odds with exciting,
579 potentially dangerous non-home settings (but not in a domestic setting).

580 Consistent with the arousal state mismatch hypothesis, we found that the

affective state produced by heroin was appraised as more pleasant when the drug was used at home than when it was when used outside the home, whereas the affective state produced by cocaine was rated as more pleasant when the drug was used outside the home then when used at home. More specifically, our data confirmed that the shift in the affective valence of heroin occurred in combination with its sedative effects, whereas the shift in the affective valence of cocaine occurred in association with its arousing effects (see Figure 3).

As discussed in the Introduction, it is reasonable to assume that the sympathomimetic effects of cocaine and the parasympathomimetic-like effect of heroin contributed to generate the respective state of emotional arousal and sedation illustrated in Figure 3 (see also: Kreibig, 2010; Levenson, 2014). Indeed, individuals with SUD report that under the influence of cocaine they experience a surge in heart rate, respiratory rate, and muscular tension, as well as a decrease in salivation, whereas when under the influence of heroin, the same individuals experience a reduction in heart rate and respiratory rate (manuscript in preparation).

The finding that even prototypical addictive drugs like heroin and cocaine do not necessarily produce a pleasurable affective state in all contexts is consistent with the theory that the mechanisms underlying the motivation to use drugs are separable from those implicated in generating drug ‘pleasure’ (Robinson and Berridge, 2008; Berridge and Kringelbach, 2013). Actually, in certain settings, almost two-thirds of experienced drug users reported that cocaine produced a mainly unpleasant affective state. This was not entirely surprising, as it has been reported previously that cocaine induces mixed (partly aversive) motivational or affective states in both rodents (Geist & Ettenberg 1997; Ettenberg et al. 1999; Knackstedt et al. 2002) and humans (Anthony et al. 1989; Geraciotti & Post 1991; Breiter et al. 1997).

Drug/setting imagery and fMRI

Whole brain analysis of BOLD signal changes during drug imagery indicated activation in several brain regions, including regions that have been previously implicated in the retrieval of memories (e.g., the angular gyrus; Bonicci et al. 2016; Kuhl and Chun 2014; Ritcher et al. 2016), in mental imagery, (e.g., the precuneus; Fletcher et al., 1995; Ritcher et al. 2016), and in brain reward (e.g., the PFCx and the striatum; Goldstein and Volkow, 2002, 2011; Cox et al., 2009; Volkow et al., 2012; Leyton and Vezina, 2013).

The working hypothesis predicted that the setting should alter in opposite directions the response of the PFCx and the striatum to heroin- versus cocaine-imagery. The double dissociation in BOLD signal changes in these regions confirmed our prediction. Interestingly, the portion of the striatum involved in the interaction was the dorsal caudate and not the ventral striatum. Previous imaging studies in drug users have reported a selective involvement of the dorsal relative to the ventral striatum (Volkow et al., 2006; Wong et al., 2006; Boileau et al., 2007; Cox et al., 2017).

Unexpectedly, the same pattern of dissociation seen in the PFCx and in the caudate was also found in the cerebellum – even though this should not have been entirely surprising given that the cerebellum is now thought to be implicated in drug addiction (for a review see Miquel et al., 2009; Moulton et al., 2014). Indeed, in the past two decades, the traditional view of the cerebellum as a primarily motor structure has been amended due to increasing evidence indicating its pivotal role in the computation of cognitive and affective processes, including: i) emotional perception

631 and encoding; ii) evaluation of emotional contexts, bodily and facial expressions, and
632 social interactions; iii) regulation of emotional states in relation to motor, cognitive,
633 and context-dependent tasks (Schmahmann, 1996, 2004; Schmahmann and Sherman,
634 1998; Scheuerecker et al., 2007; Stoodley, 2012; Buckner, 2013; Adamaszek et al.,
635 2014, 2017; Van Overwalle et al., 2015). Cerebellar-dependent behavioral and
636 emotional disorders have been conceptualized “as either excessive or reduced
637 responses to the external or internal environment” (Schmahmann et al., 2007).
638 Indeed, both positive and negative emotions are thought to be processed by cerebellar
639 circuits (Turner et al., 2007; Baumann and Mattingley, 2012). An rCBF PET study
640 has shown that craving is associated to activation of the left posterior cerebellum
641 (Kilts et al., 2001) and cerebellar activity in heroin users has been correlated with self-
642 reports of negative emotions, such as ‘feeling tense’ and ‘withdrawal symptoms’
643 during cue evoked craving (Sell et al., 2000). These findings support the idea that
644 cerebellar activation may reflect aversive processing that is not specific to drug
645 craving. In this respect, it is important to notice that the cerebellum is interconnected
646 with the striatum (Hoshi et al., 2005), which is implicated in processing not only
647 rewarding but also aversive stimuli (Ungless et al., 2004; Schultz, 2007; Leknes and
648 Tracey, 2008), particularly the dorsal striatum (Delgado et al., 2003; Seymour et al.,
649 2007; Gorka et al., 2017). This perspective might also help explaining why the
650 BOLD signal in the caudate, PFCx, and cerebellum increased more when the
651 participants imagined using heroin outside the home and cocaine at home (that is, in
652 the presence of a mismatch) than when they imagined using heroin at home and
653 cocaine outside the home. Although the relationship between BOLD signal and
654 underlying neural events is far from simple (Logothetis, 2008), it is possible that the
655 fMRI data reflect the engagement of a fronto-striatal-cerebellar network in processing

the negative affective state produced by a mismatch between drug effects and external environment.

Another interesting feature of our results is that the pattern of activation in most regions was lateralized to the left hemisphere, consistent with previous fMRI studies concerning memory retrieval (Spaniol et al., 2009).

Conclusions

In summary, we report here that setting of drug use exerts a substance-specific influence not only on the affective response to heroin and cocaine but also on the activity of brain regions implicated in processing drug reward and contextual information in humans, consistent with previous findings in the rat (Badiani et al., 1998, 1999; Uslander et al. 2001a, 2001b; Ferguson et al., 2004; Hope et al., 2006; Paolone et al., 2007; Celentano et al., 2009). The within-subject design of our study makes it especially compelling because the results cannot be ascribed to individual differences drug availability, peer influence, or other socio-demographic factors.

The procedures used in this study were based on retrospective reports and emotional imagery, given that it would have been next to impossible to administer alternatively heroin and cocaine to the same individual during the same fMRI procedure (and certainly not in real-world settings, which was our main focus of investigation). In addition, because of methodological constraints, we did not measure affective or autonomic responses to drug imagery during fMRI. To overcome these limitations, novel methodologies should be developed in order to elucidate the interoceptive and exteroceptive components of drug-setting interactions

and dissect the exact role of relevant brain networks.

Finally, more research is necessary to verify whether the context can shape initial drug use and vulnerability to relapse in humans, as previously shown in rats (Caprioli et al., 2007b, 2008; Montanari et al. 2015). Nevertheless, by emphasizing the distinctive effects of different classes of drugs and the importance of the context of drug use, our study has potential therapeutic implications, especially for the prevention of relapse in real world settings via Ecological Momentary Interventions (see Epstein et al., 2009).

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Table 1. Socio-demographic information and diagnostic characteristics of the study sample for Experiment 1 (n=53).

	Mean (SD) or %
Drug use	
• Heroin and cocaine	84.91%
• Heroin only	1.89%
• Cocaine only	13.21%
Age (years)	37.11 (10.42)
Sex/gender (females)	21%
Education (years) ^a	11.21 (3.47)
Ethnicity	
▪ Caucasian	88.68%
▪ Multiethnic	7.55%
▪ Black/African	1.89%
▪ Indian/Pakistani/Bangladeshi	1.89%
Employment status ^a	
▪ Employed	46.34%
▪ Retired/Disability	9.76%
▪ Controlled environment	9.76%
▪ Unemployed	34.15%
Fixed Residence	86.79%
Household	
▪ Family/partner	82.61%
▪ Alone	10.87%
▪ Flat mates	6.52%
City of residence (no. inhabitants)	
▪ <100.000	90.57%
▪ 10.000-100.000	9.43%
Methadone program ^b	84.91%
mg/day	55.91 (57.24)
Heroin	n=46
▪ Years of use	15.96 (10.31)
▪ Main route of administration	
• Intravenous injection	54.35%
• Inhalation (smoked)	23.91%
• Insufflation (snorted)	21.74%
Cocaine	n=52
▪ Years of use	14.44 (8.51)
▪ Main route of administration ^c	
• Intravenous injection	26.00%
• Inhalation (smoked)	26.00%
• Insufflation (snorted)	48.00%

a. 12 missing data; b. 11 missing data; c. 2 missing data.

997 **Table 2.** Socio-demographic information, diagnostic characteristics and pre-scan data
 998 for Experiment 2 (n=20).
 999

	Mean (SD) or %
Age (years)	35.35 (8.13)
Education (years)	13.60 (3.31)
Employed	85%
Handedness (left/ambidextrous/right)	5%/0%/95%
Methadone program mg/day	95% 39.47 (30.00)
Heroin <ul style="list-style-type: none"> ▪ Years of use ▪ Age of first use^a ▪ Main route of administration <ul style="list-style-type: none"> • Intravenous injection • Inhalation (smoked) • Insufflation (snorted) 	13.20 (6.29) 20.39 (4.30) 55% 35% 10%
Cocaine <ul style="list-style-type: none"> ▪ Years of use ▪ Age of first use^a ▪ Main route of administration <ul style="list-style-type: none"> • Intravenous injection • Inhalation (smoked) • Insufflation (snorted) 	15.25 (5.73) 18.83 (6.86) 35% 10% 55%
Pre-scan drug positive^b <ul style="list-style-type: none"> ▪ Methadone ▪ Morphine/opiates ▪ THC ▪ Benzodiazepines ▪ Cocaine ▪ Barbiturates ▪ Amphetamine ▪ Methamphetamine 	90% 65% 55% 20% 20% 0% 0% 0%
Training Imagery Questionnaires <ul style="list-style-type: none"> ▪ VVIQ ▪ VMIQ ▪ TVIC ▪ IIES–Positive emotional states ▪ IIES–Negative emotional states 	% participants with >50% of max. score 90% 90% 95% 90% 90%
VVIQ, Vividness of Visual Imagery Questionnaire; VMIQ, Vividness of Movements Imagery Questionnaire; TVIC, Test of Visual Imagery Control; IIES; Imagery Induction of Emotional States (adapted version).	

1000 a. 2 missing data, b. 1 missing data.

1001 **Table 3. fMRI Imagery scripts.**

1002

BASELINE IMAGERY AT HOME	BASELINE IMAGERY OUTSIDE THE HOME
1) Imagine as vividly as possible that you are at home. 2) Imagine you are relaxing at home.	1) Imagine as vividly as possible that you are in a club. 2) Imagine you are relaxing in the club.
DRUG IMAGERY AT HOME	DRUG IMAGERY OUTSIDE THE HOME
1) Imagine as vividly as possible that you are at home. 2) Imagine using heroin at home. or 1) Imagine as vividly as possible that you are at home. 2) Imagine using cocaine.	1) Imagine as vividly as possible that you are in a club. 2) Imagine using heroin in the club. or 1) Imagine as vividly as possible that you are in a club. 2) Imagine using cocaine in the club.

1003

Table 4. Brain Activation during drug-imagery. Whole brain analysis revealed significant activation during drug imagery (relative to baseline imagery), for at least one of the four drug-setting conditions, in the clusters listed below ($P_{FWE} < 0.05$ at the voxel level). Post-hoc analyses indicated significant drug x setting x time interaction in the regions indicated in bold (see text for details).

<i>Cluster</i>	<i>Anatomical region</i>	<i>Extent (voxels)</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>Peak F</i>	<i>Peak Z</i>
1	L. Mid. Frontal gyrus (BA8)	7	-24	17	64	13.44	5.45
2	L. Mid. Frontal gyrus (BA46)	4	-33	56	19	11.24	4.98
3	L. BA6, BA44, BA45	171	-51	26	25	17.64	6.20
	L. Mid. Frontal gyrus (BA44)	69	-39	11	34		
	L. Precentral gyrus (BA6)	14	-36	2	61		
	L. Inf. Frontal gyrus (BA45)	88	-51	26	25		
4	L. Inf. Frontal gyrus (BA45)	17	-48	44	7	14.14	5.59
5	L. Suppl. Motor area (BA32)	8	-6	20	46	12.07	5.16
6	L. Post. Cingulum	24	-3	-34	31	15.01	5.75
7	L. Inf. Parietal lobe (BA40)	170	-36	-58	40	16.60	6.30
8	L. Angular gyrus	19	-57	-46	28	12.81	5.32
9	L. Precuneus (BA7)	19	-9	-67	43	14.99	5.75
10	L. Mid. Temporal gyrus (BA21) post.	28	-63	-43	-5	17.85	6.23
11	L. Mid. Temporal gyrus (BA21) ant.	70	-60	-13	-11	14.71	5.70
12	R. Mid. Temporal gyrus (BA21) ant.	194	51	-25	-8	26.27	7.34
13	L./R. Caudate/Thalamus	245	0	-10	10	16.51	6.02
	L. Caudate	62	-18	5	19		
	L. Thalamus	64	-3	-10	10		
	R. Caudate	38	18	5	16		
	R. Thalamus	52	3	-7	7		
14	L. Cerebellum (Crus I/II)	118	-36	-61	-32	17.85	6.23
15	R. Cerebellum (Crus I/II)	224	15	-79	-35	20.23	6.59
16	L. Brain stem	11	-3	-28	-14	13.77	5.52
17	R. Brain stem	7	15	-25	-11	12.23	5.20

1011 **Table 5. Brain Activation during drug-imagery.** Three-way, repeated measure,
 1012 ANOVA revealed drug x setting ($F_{1,19}$) and drug x setting x time ($F_{11,209}$) interactions,
 1013 and corresponding effect size (η_p^2), in the brain regions listed below.

1014

Anatomical region	Effect/Interaction	F	P (uncorrected)	P (Bonferroni's correction)	η_p^2
L. BA 44	drug x setting	4.879	0.004	0.08	0.361
	drug x setting x time	10.719	<0.0001	<0.01	0.223
L. Caudate	drug x setting	4.208	0.054	0.70	0.181
	drug x setting x time	3.918	<0.0001	<0.01	0.171
L. Cerebellum	drug x setting	6.452	0.020	0.36	0.254
	drug x setting x time	3.382	<0.0001	<0.01	0.151
R. Cerebellum	drug x setting	7.907	0.011	0.22	0.294
	drug x setting x time	5.812	<0.0001	<0.01	0.234

1015

Figure legends

Figure 1. Assessment of affective states. **A.** Graphic representation of the Circumplex Model of Affect (Russell 1980). **B.** Bidimensional representation of affective states used in Experiment 1. This test was developed based on the Circumplex Model of Affect illustrated in the left panel, by removing the labels indicating different levels for each dimension, and by adding emoticons.

Figure 2. Outline of the imagery task during fMRI and vividness ratings. **A.** Outline of the 8 imagery trials during fMRI (2 for each combination of drug and setting). Each trial began with a baseline imagery period of 60 s, during which the participant were asked to imagine relaxing either at home or outside the home. The participants were then asked to imagine using heroin or cocaine in the baseline setting for 120 s (drug imagery). This period was followed by 60 s of rest, during which the participants were asked not to engage in imagery. Finally, the participants were asked to rate the vividness of the imagery on a VAS (1-10 points), by pressing a button. Immediately after completing the VAS the next trial began. **B.** Vividness ratings for individual participants.

Figure 3. Subjective appraisal of the emotional valence of drug experience as a function of drug and setting. The pie charts show the proportion of participants reporting the affective states detailed in the legend and illustrated in Figure 6 (see text for details) after heroin (**A** and **B**) or cocaine (**C** and **D**) use. The McNemar's test indicated significant shifts in valence as a function of the setting of drug use. Notice that a small proportion of participants reported two affective states (hatched lines) or more (grey).

Figure 4. Whole brain analysis map. The map shows regions of significant neuronal activation during the drug imagery period, irrespective of drug and setting, relative to the baseline imagery period. Whole brain analysis conducted in SPM8 using an “omnibus” F contrast revealed significant changes in the regions showed below ($P_{FWE} < 0.05$ at the voxel level). Voxels below threshold are not rendered in color.

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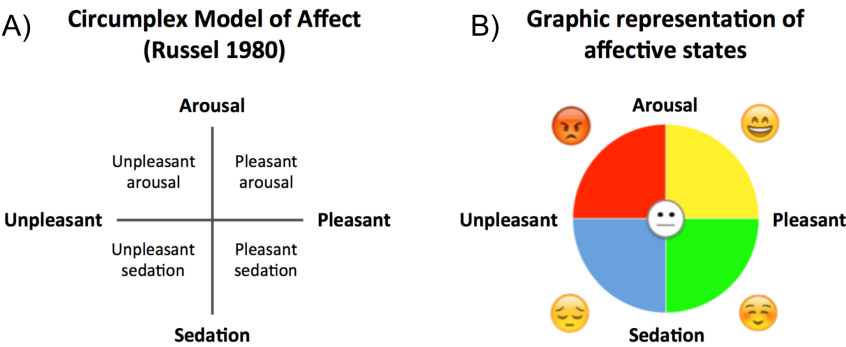
1051 **Figure 5. BOLD signal changes in the left PFCx.** Mean (\pm SEM) BOLD signal
1052 changes **(A)** during the drug imagery task (relative to baseline imagery) in the BA 46,
1053 BA 44, and BA 8 obtained by averaging the values of 12 10-s bins calculated using
1054 FIR analysis **(B)**. The whole brain map is the same shown in Fig. 4.

1055

1056 **Figure 6. BOLD signal changes in the left caudate and in the cerebellum.** Mean
1057 (\pm SEM) BOLD signal changes **(A)** during the drug imagery task (relative to baseline
1058 imagery) in the caudate and cerebellum obtained by averaging the values of 12 10-s
1059 bins calculated using FIR analysis **(B)**.

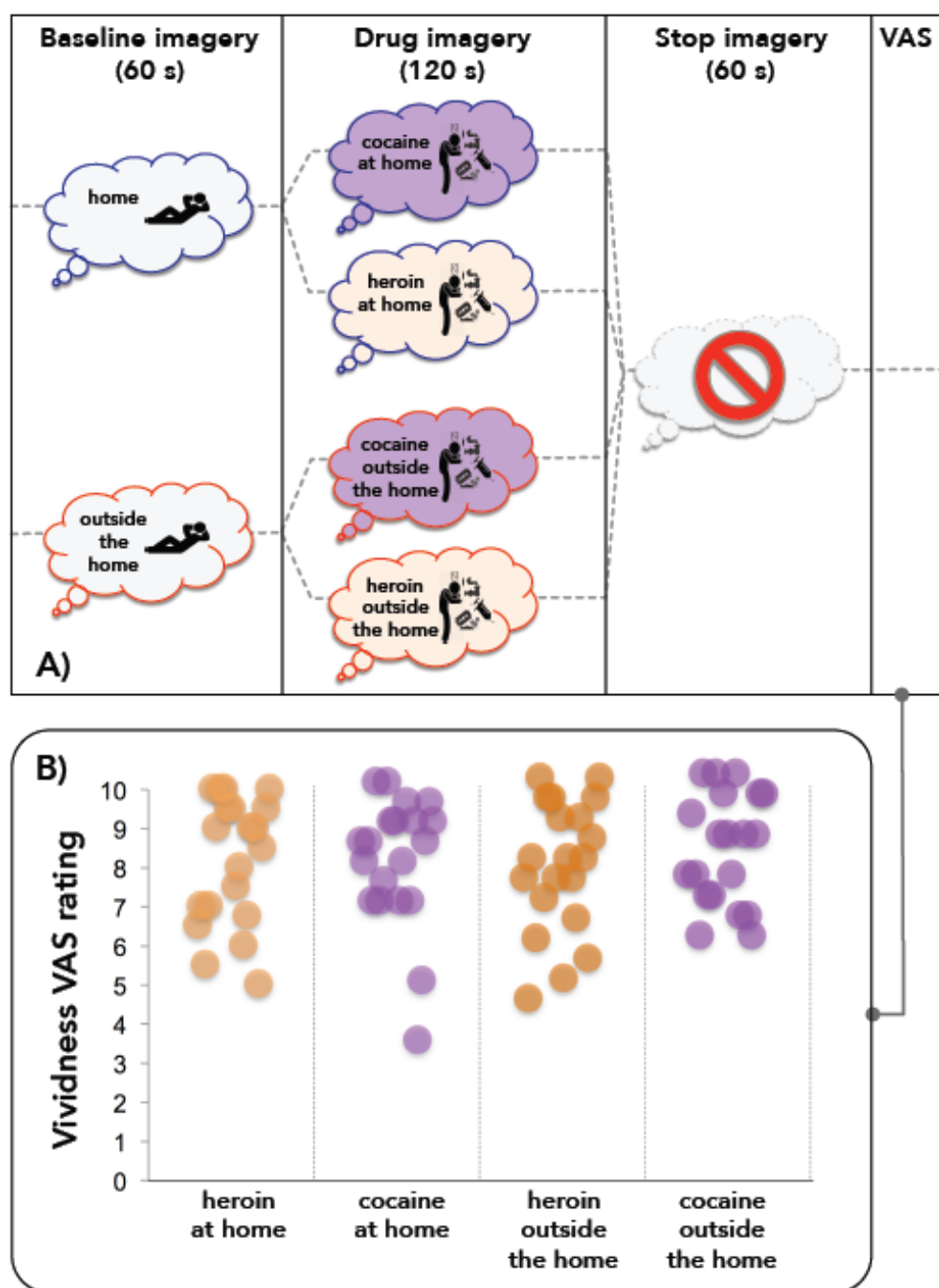
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1061 Fig. 1
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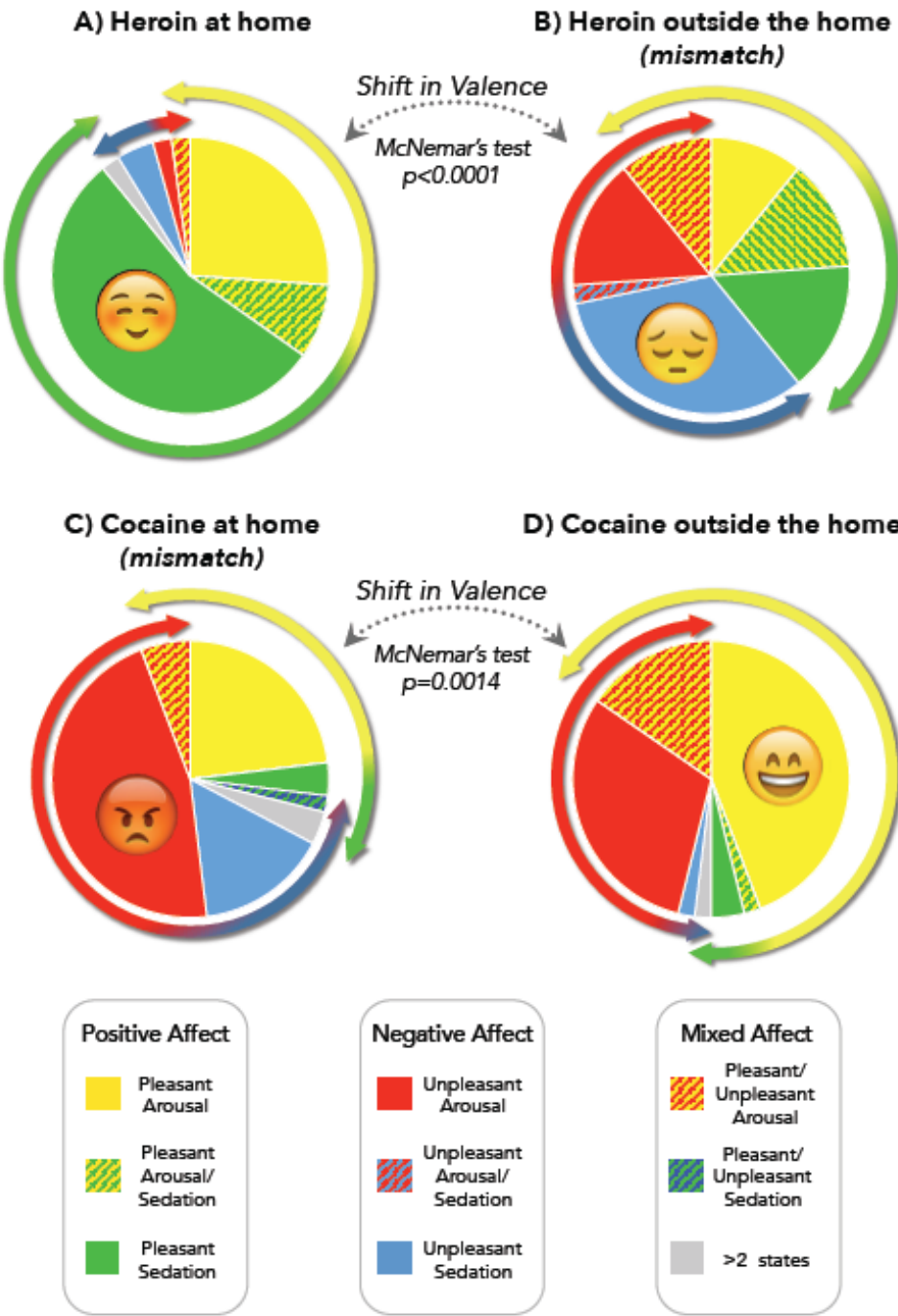
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1065 Fig. 2
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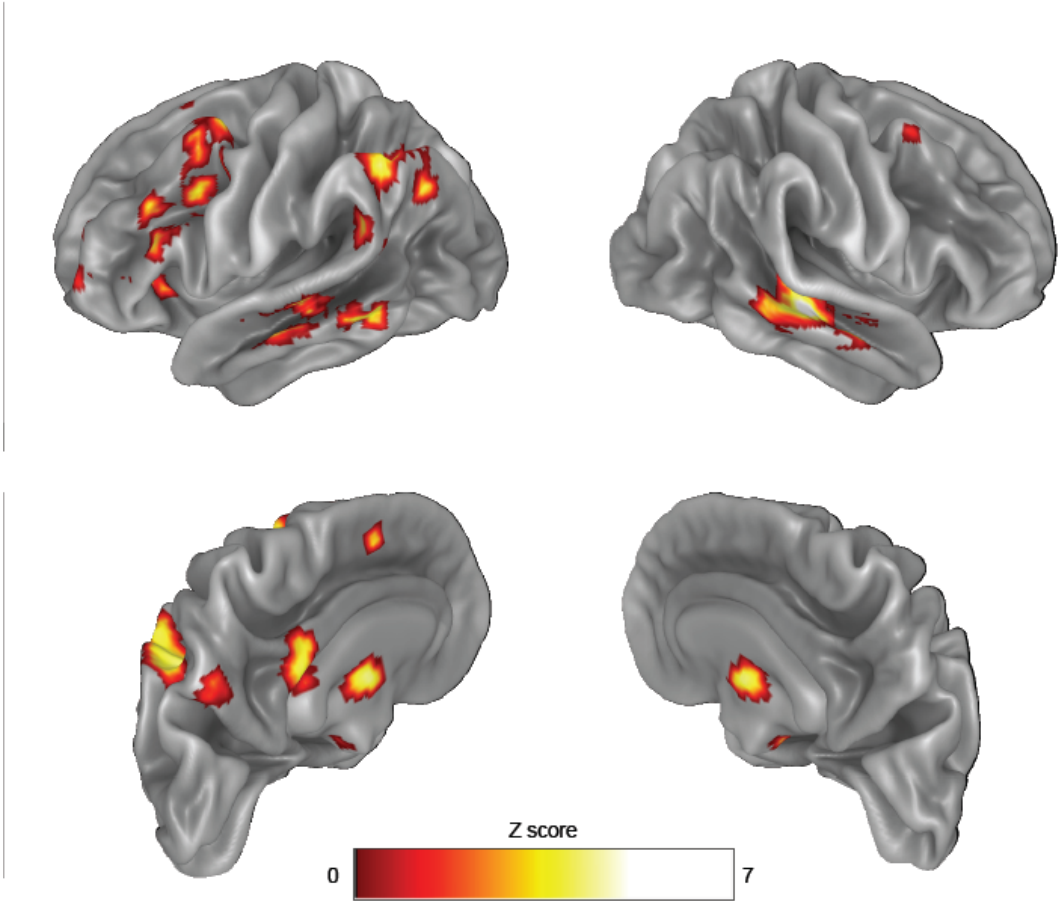
1069 Fig. 3
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1073 Fig. 4

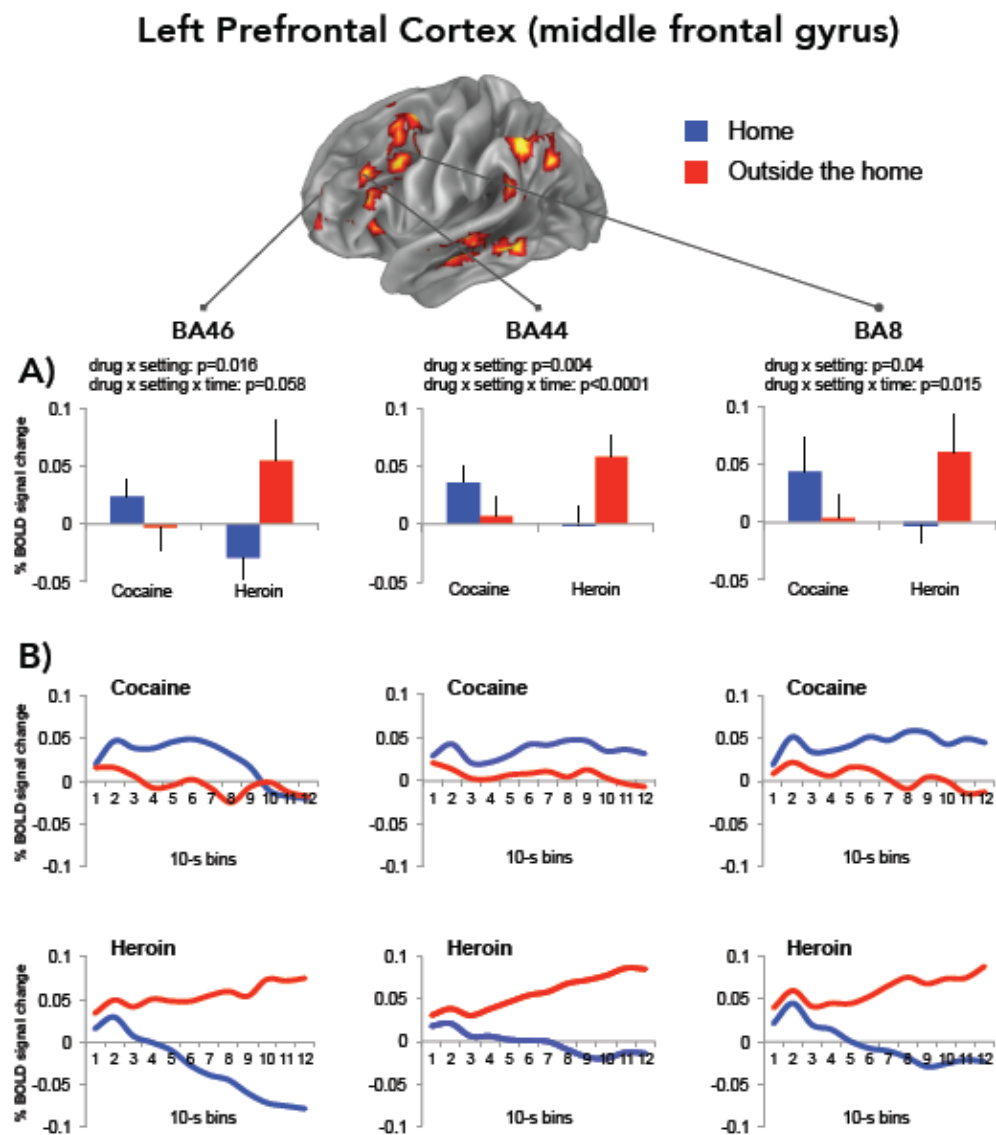
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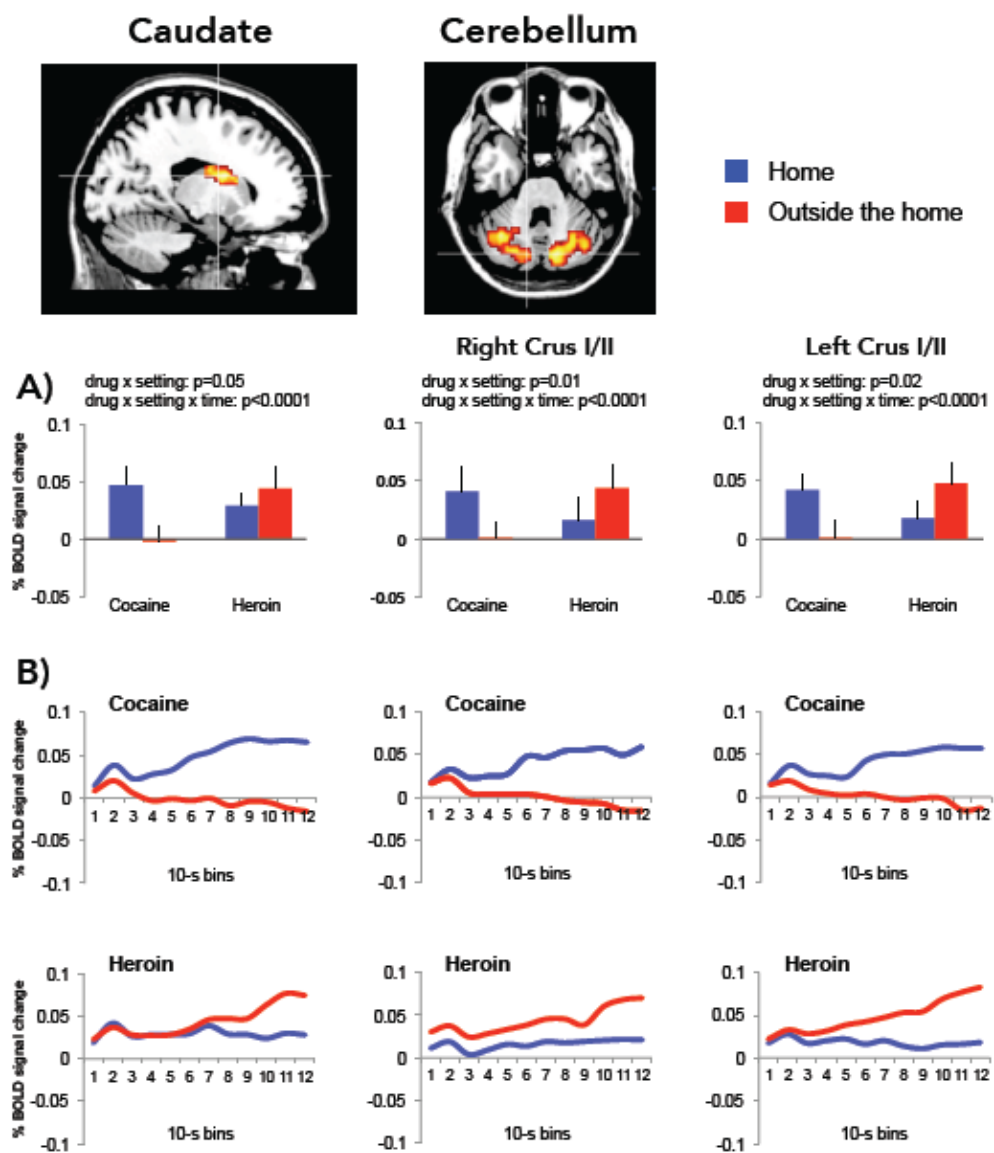
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1077 Fig. 5
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1081 Fig. 6
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